# Dengue Score
# การวินิจฉัยโรคติดเชื้อไวรัสเดงกี่อย่างง่ายและแม่นยำในประเทศที่มีทรัพยากรจำกัด
# Dengue Score
# A Simple and Highly Specific Test for Diagnosis of Dengue Infection in Resource-limited Settings

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**บทคัดย่อ**

**วัตถุประสงค์:** เพื่อศึกษาลักษณะทางคลินิกและการตรวจทางห้องปฏิบัติการที่ง่ายและจำเพาะในการวินิจฉัยแยกโรคติดเชื้อไวรัสเดงกี่กับโรคติดเชื้อฉับพลันอื่นๆ ในประเทศที่มีทรัพยากรจำกัด

**วัสดุและวิธีการศึกษา**: เป็นการศึกษาไปข้างหน้าในโรงพยาบาลนครปฐม โรงพยาบาลตติยภูมิ ขนาดเตียง 670 เตียง ระหว่างวันที่ 1 สิงหาคม ถึง 31 ตุลาคม 2558 กลุ่มตัวอย่างที่เลือกเข้าทำการศึกษาคือ ผู้ป่วยผู้ใหญ่ มีไข้ฉับพลัน และแพทย์ผู้ดูแลสงสัยโรคติดเชื้อไวรัสเดงกี่ นำมาวิเคราะห์หาปัจจัยทางคลินิกในการวินิจฉัยโรคติดเชื้อไวรัสเดงกี่

**ผลการศึกษา:** ผู้ป่วยทั้งสิ้น 155 ราย อายุเฉลี่ย 33.5 ± 17.1 ปี ร้อยละ 51 เป็นเพศหญิง พบการติดเชื้อไวรัสเดงกี่ 113 ราย (ร้อยละ 73) และการติดเชื้ออื่นๆ 42 ราย (ร้อยละ 27) ปัจจัยทำนายการติดเชื้อไวรัสเดงกี่ ได้แก่ การไม่มีอาการไอ (OR 0.3, 95%CI 0.1;0.9, $p$ = 0.04), WBC ≤ $4x10^3/mm^3$ (OR 4.6, 95%CI 1.2;17.0, $p$ 0.02), platelet ≤ $100x10^3/mm^3$ (OR 6.6, 95%CI 1.5;29.8, $p$ = 0.01) และ ESR ≤ 20 mm/hr (OR 3.3, 95%CI 1.01;12.3, $p$ = 0.047) เมื่อนำปัจจัยดังกล่าวมาวิเคราะห์หา Dengue Score โดยการไม่มีปัจจัยดังกล่าวให้คะแนน = 0 และการมีปัจจัยดังกล่าวให้คะแนน = 1 ได้ดังนี้ (-1.3xcough) + (1.5xWBC<$4X10^3/mm^3$) + (1.9xplatelet<$100x10^3/mm^3$) + (1.2xESR<20) โดยถ้า Dengue score มากกว่าหรือเท่ากับ 2 จะสามารถใช้วินิจฉัยโรคติดเชื้อไวรัสเดงกี่ได้มีความไว ความจำเพาะ ค่าทำนายผลบวก และค่าทำนายผลลบ เท่ากับร้อยละ 58, ร้อยละ 95, ร้อยละ 98 และร้อยละ 38 ตามลำดับ

**สรุป:** อาการและอาการแสดงของโรคติดเชื้อไวรัสเดงกี่คล้ายกับการติดเชื้อฉับพลันอื่นๆ แยกออกจากกันได้ยาก Dengue Score สามารถใช้ในการวินิจฉัยโรคติดเชื้อไวรัสเดงกี่ได้อย่างแม่นยำในประเทศที่มีทรัพยากรจำกัด

**คำสำคัญ : ค่าการทำนาย การวินิจฉัย โรคติดเชื้อไวรัสเดงกี่ ประเทศที่มีทรัพยากรจำกัด**
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## ABSTRACT

**Objective:** To determine the simple and specific clinical predictors to discriminate dengue infection from other acute febrile illnesses in resource-limited settings.

**Material and methods:** Prospective study was conducted at Nakhonpathom Hospital, a 670-bed tertiary care hospital in Thailand during August 1 and October 31, 2015. The inclusion criteria were adults who presented with acute fever, clinically suspected to be dengue infection by attending physician. Predictive factors for dengue infection were analysed.

**Result:** There were 155 patients. Mean age was 33.5 ± 17.1 yrs and 51% were female. One hundred and thirteen patients (73%) had dengue and 42 (27%) had non-dengue. Factors associated with dengue including absence of cough (OR 0.3, 95%CI 0.1;0.9, $p$ = 0.04), WBC ≤ $4x10^3/mm^3$ (OR 4.6, 95%CI 1.2;17.0, $p$ 0.02), platelet ≤ $100x10^3/mm^3$ (OR 6.6, 95%CI 1.5;29.8, $p$ = 0.01) and ESR ≤ 20 mm/hr (OR 3.3, 95%CI 1.01;12.3, $p$ = 0.047). Dengue score was calculated as follows (variables coded as absence = 0, presence =1): (-1.3xcough) + (1.5xWBC<$4X10^3/mm^3$) + (1.9xplatelet<$100x10^3/mm^3$) + (1.2xESR<20). A score ≥ 2 was the best cut-off point for predicting dengue with sensitivity, specificity, PPV and NPV of 58%, 95%, 98% and 38%, respectively.

**Conclusions:** Clinical presentation of dengue was similar to other acute febrile illnesses. Dengue score provides a very high specificity and PPV and can be used to diagnose dengue infection in resource-limited settings.

**Keywords: predicting score, diagnosis, dengue infection, resource-limited settings**
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## Introduction

Dengue is the most important mosquito-borne viral infection in Thailand and the tropics.[1-5] At least 100 countries with 2.5 billion people or 40% of world's population are at risk of dengue virus transmission.[6]

Early diagnosis and proper treatment were associated with outcome. Clinical presentations of dengue infection were nonspecific and similar to other acute febrile illnesses (AFI) such as primary bacteremia, rickettsial or malaria infection.[7-14] Leukopenia, thrombocytopenia, atypical lymphocytosis are common in dengue infection, but can be found in other viral infections. Virologic and serologic testings can be used for diagnosis,[15] however they are not available to many resource-limited healthcare settings.

Previous studies have identified simple clinical and laboratory features to distinguish dengue from other AFI. These included complete blood counts, serum aspartate aminotransferase

(AST), serum alanine aminotransferase (ALT), coagulation tests, erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP).[7-13, 15-17]

Leukopenia and thrombocytopenia occur as results of bone marrow suppression and peripheral destruction during acute dengue infection.[18] Liver involvement is frequently observed with varying degree of liver injury.[19-20] The common abnormalities include increased AST, ALT and AST/ALT ratio. Coagulation abnormalities have been found in dengue patients. Prolongation of activated partial thromboplastin time (aPTT) with normal prothrombin time (PT) is frequently found, suggestion of a sequence of defect in intrinsic partway of coagulation.

Acute phase reactants such as ESR and CRP have been used as a marker of an inflammation and an infection. Earlier reports documented normal ESR in dengue illness.[16-17] CRP has been used to distinguish viral infection from bacterial infection as well as dengue from malaria. In addition, the level of CRP was lower among patients with dengue.[7,12] However, the optimal cutoff of these two tests have not been defined.

The objective of the study was to determine clinical predictors to discriminate dengue infection from other AFI and generate dengue score for prediction the diagnosis of dengue infection.

## Material and methods

All consecutive patients were prospectively enrolled at Nakhonpathom Hospital, a 670-bed tertiary care hospital in Thailand during August 1 and October 31, 2015.

Patients were included if they met all of the following criteria: ≥15 years of age, documented fever of 38.0°C or higher at presentation or history of fever that had persisted for 1–7 days without an identified source, and attending physicians suspected dengue.

Patients were excluded if they had immunologic/hematologic disorders, had severe lung/heart/liver disease, were receiving corticosteroid/immunosuppressive/anticoagulant therapy, had HIV infection and had dengue infection with other infection at the same admission.

Detailed history of each patient was taken including age, sex, days of fever and presenting symptoms (headache, myalgia, nausea and vomiting, arthralgia, retro-orbital pain, cough and rash). Blood samples were drawn within 24 hours of admission for complete blood count, ESR, CRP, PT, aPTT, liver and kidney function tests.

The diagnosis of dengue was based on the presence of either dengue NS1 antigen or IgM antibiody by a commercially rapid dengue diagnostic kit, the SD BIOLINE Dengue Duo combo device (Standard diagnostic inc., Korea). The sample size of the study was based on an estimated 54.4% and 23% prevalence of leukopenia and thrombocytopenia among patients with and without dengue infection. The required total sample size was calculated to be 214 patients.

$$n = \frac{[Z_{\alpha/2}\sqrt{2P(1-P)}+Z_{\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}]^2}{(p_1-p_2)^2}$$

$$P = \frac{(p_1+p_2)}{2} = \frac{(0.544+0.23)}{2} = 0.387$$

$$n = \frac{[1.96\sqrt{2(0.387)(1-(0.387))}+0.84\sqrt{0.544(1-0.544)+0.23(1-0.23)}]^2}{(0.544-0.23)^2}$$

The study was approved by the Human Ethics Review Committee of Nakhonpathom Hospital (COA no. 004/2015)

## Statistical analysis

Firstly, descriptive analysis was conducted to calculate number, percentage mean and standard deviation. Secondly, Fisher's exact test and t-test were used for determination of associations between independent variable and dengue infection. Finally, multiple logistic regression analysis was used to determine the significant predictors related to dengue infection ($p<0.05$). All variables statistically significant at p-value < 0.1 in Fisher's exact and t-test were included in the multivariable logistic models.

## Results

The study was stopped after enrollment of 155 patients because of end of dengue outbreak during study period. The mean age of patients was 33.5 ± 17.1 years and 79 (51%) were female. Median duration of fever at hospital admission was 3 (range 1-7) days. The most presenting symptoms were fever (100%) and nausea/vomiting (52%).

One hundred and thirteen (73%) and 42 (27%) patients had dengue and non-dengue infection, respectively. Patients with dengue were less likely to have cough at presentation (23% vs 41%, *p* 0.05), more commonly to have decreased WBC (3.8±1.9 vs 6.1±3.5 x $10^3$/$mm^3$, $p < 0.001$), decreased platelet (102.6±61.3 vs 148.7±67.2 x $10^3$/$mm^3$, $p < 0.001$), increased AST level (138±141 vs 53±43, *p* 0.05), low ESR (23.7±19.2 vs 33.4±21.1 mm/hr, *p* 0.05) and decreased CRP (16.0±15.6 vs 37.4±46.4 mg/L, *p* 0.001). Level of hematocrit, percentage of neutrophil, percentage of lymphocyte, albumin, ALT, PT and PTT were not different significantly between two groups (table 1).

**Table 1** Factors associated with dengue infection

| Variable | Total (n = 155) | Dengue infection | | *P*-value |
|---|---|---|---|---|
| | | Dengue (n =113) | Not dengue (n = 42) | |
| Mean age, years (±S.D.) | 33.5 (17.1) | 32.6 (16.9) | 35.8 (17.6) | 0.30 |
| Female | 79 (51%) | 59 (52%) | 20 (48%) | 0.59 |
| Median day of fever at presentation, days (min;max) | 3 (1;7) | 3 (1;7) | 3 (1;7) | 0.19 |
| Median duration of fever, days (min;max) | 5 (1;11) | 5 (3;11) | 4 (1;6) | <0.001 |
| Nausea/vomiting | 81 (52%) | 60 (53%) | 21 (50%) | 0.55 |
| Cough | 43 (28%) | 26 (23%) | 17 (41%) | 0.05 |
| Mean hematocrit, % (±S.D.) | 43 (32) | 43.3 (32) | 45 (36) | 0.44 |
| Mean WBC, cellsx$10^3$/$mm^3$ (±S.D.) | 4.4 (2.5) | 3.8 (1.9) | 6.1 (3.5) | <0.001 |
| WBC ≤ 4 x$10^3$/$mm^3$ | 87 (56%) | 75 (66%) | 10 (24%) | 0.02 |
| Mean neutrophil, % (±S.D.) | 63 (15) | 63 (15) | 65 (17) | 0.53 |
| Mean lymphocyte, % (±S.D.) | 28 (12) | 28 (12) | 27 (13) | 0.60 |
| Mean platelet, cellsx$10^3$/$mm^3$ (±S.D.) | 113.2 (65.5) | 102.6 (61.3) | 148.7 (67.2) | <0.001 |
| Platelet ≤ 100 x$10^3$/$mm^3$ | 68 (44%) | 59 (52%) | 30 (71%) | 0.01 |
| Mean AST, IU/L (±S.D.) | 117 (129) | 138 (141) | 53 (43) | 0.05 |
| Mean ALT, IU/L (±S.D.) | 66 (68) | 75 (74) | 38 (34) | 0.10 |
| Mean albumin, mg/dL (±S.D.) | 3.9 (0.4) | 3.9 (0.3) | 3.9 (0.6) | 0.89 |
| Mean PT, sec (±S.D.) | 13.2 (2.9) | 13.3 (3.3) | 12.8 (1.1) | 0.70 |
| Mean PTT, sec (±S.D.) | 34.0 (5.1) | 34.7 (5.1) | 31.4 (4.5) | 0.13 |
| Mean ESR, mm/hr (±S.D.) | 25.9 (19.9) | 23.7 (19.2) | 33.4 (21.1) | 0.05 |
| ESR ≤ 20 mm/hr | 91 (59%) | 75 (66%) | 15 (36%) | 0.03 |
| Mean CRP, mg/L (±S.D.) | 20.3 (26.2) | 16.0 (15.6) | 37.4 (46.4) | 0.001 |

Multivariate analysis was performed by a stepwise logistic regression analysis. Four factors were associated with dengue; absence of cough (OR 0.3, 95%CI 0.07;0.96, *p* 0.04), WBC < 4 x $10^3$/$mm^3$ (OR 4.6, 95%CI 1.2;17.0, *p* 0.02), platelet < 100 x $10^3$/$mm^3$ (OR 6.6, 95%CI 1.5;29.8, *p* 0.01) and ESR ≤ 20 mm/hr (OR 3.3, 95%CI 1.01;12.3, *p* 0.047) (table 2).

**Table 2** Multiple logistic regression of factors predicting dengue infection

| Factors | Adjusted OR (95% CI) | Coefficient | *P-value* |
|---|---|---|---|
| Absence of cough | 0.3(0.1;0.9) | -1.3 | 0.04 |
| WBC ≤ 4 $x10^3/mm^3$ | 4.6(1.2;17.0) | 1.5 | 0.02 |
| Platelet ≤ 100 $x10^3/mm^3$ | 6.6(1.5;29.8) | 1.9 | 0.01 |
| ESR ≤ 20 mm/hr | 3.3(1.01;12.3) | 1.2 | 0.047 |

The prediction score was calculated from (-1.3 x cough) + (1.5 x leucocyte < 4 x $10^3/mm^3$) + (1.9 x platelet < 100 x $10^3/mm^3$) + (1.2 x ESR ≤ 20), when 1 used for the presence and 0 for the absence of each factors.

The score showed an area under the curve of 0.85 (95%CI 0.75-0.94) (figure 1). Using a cut-off ≥ 2, sensitivity, specificity, positive predictive value and negative predictive value in predicting dengue infection were 58.0%, 94.6%, 97.6 and 37.8, respectively.

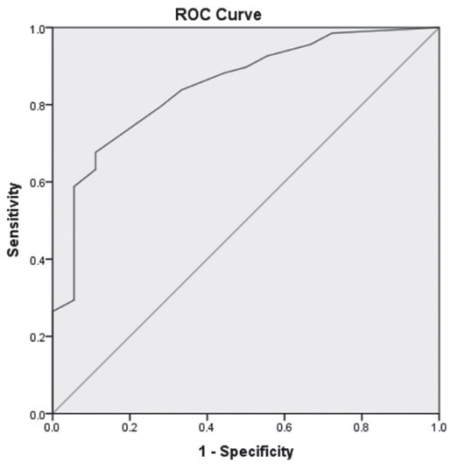


**Fig. 1** ROC curve for diagnosis of dengue infection

## Discussion

Early in the course of disease, clinical manifestations of dengue are indistinguishable to other kinds of AFI. The use of this score for diagnosing dengue promises to provide rapid and accurate diagnosis. The PPV of dengue score in this study was higher than those identified by previous retrospective studies (98% compared to 88% and 93%).[7,8]

Another potential strength of this score is its simplicity. It is based on one clinical manifestation and three easily laboratory parameters which commonly available in most healthcare settings in Thailand. The presence

of cough is the only manifestation that differ between two groups. Previous studies did not identify this finding.[8,12] Influenza season occurred during the study period and could explain why this symptom was manifested more commonly among non-dengue group.

A previous report demonstrated the difference in clinical features of dengue between elderly and younger adults.[21] Elderly patients had less classical dengue symptoms such as headache, myalgia and bone pain. There were 12 elderly patients in our study (age above 65 years). This may be one possible explanation while there was no statistical significance among clinical presentations.

As previous reports, this study confirmed the association between dengue and the presence of leukopenia and thrombocytopenia which are the most prevalent findings of dengue infection.[18]

ESR and CRP have been recognized as an indicator of various inflammations. Earlier studies demonstrated that ESR was within normal limits in dengue infection and could help to discriminate dengue infection to various bacterial infections.[16-17] CRP was significantly associated with dengue diagnosis in the univariate analysis, however it lost its significance in the multivariate analysis.

Patients with dengue in the study also showed a trend toward higher AST, ALT, aPTT levels than the other group, but the difference was not statistically significant.

A limitation of the study was the relatively small sample size. The study was stopped after enrollment of 155 patients because of end of dengue outbreak during study period. In addition, we included only hospitalized patients. Therefore, the results of the study may not be generalized to general populations. Further studies with appropriate sample size are needed.

Despite the limitation of study, this newly developed score using a combination of 1 clinical feature and 3 laboratory parameters is rapid, simple and inexpensive. Dengue score ≥2 is highly specific and has a high PPV and therefore can potentially use as a screening tool for early diagnosis of dengue.

## Conclusion

Clinical presentation of dengue infection was similar to other AFI. This prediction score provides a very high specificity and PPV and can be used as predictive markers for early diagnosis of dengue infection in resource-limited healthcare settings.

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## References

1. Leelarasamee A, Chupaprawan C, Chenchittikul M, et al. Etiologies of acute undifferentiated febrile illness in Thailand. J Med Assoc Thai 2004;87(5):464-72.
2. Suttinont C, Losuwanaluk K, Niwatayakul K, et al. Causes of acute, undifferentiated, febrile illness in rural Thailand: results of a prospective observational study. Ann Trop Med Parasitol 2006;100(4):363-70.
3. Mackenzie JS, Gubler DJ, Petersen LR. Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. Nat Med 2004;10(12 Suppl):S98-S109.
4. อมร ลีลารัศมี. ไข้ฉับพลันที่ไม่ทราบสาเหตุ. ใน: นลินี อัศวโภคี, บรรณาธิการ. ประสบการณ์ด้านโรคติดเชื้อในประเทศไทย. พิมพ์ครั้งที่ 2. กรุงเทพฯ: สมาคมโรคติดเชื้อแห่งประเทศไทย; 2542. หน้า 1-12.
5. Capeding MR, Chua MN, Hadinegoro SR, et al. Dengue and other common causes of acute febrile illness in Asia: an active surveillance study in children. PLoS Negl Trop Dis 2013;7(7):e2331.
6. World Health Organization, Regional Office for South-East Asia. Dengue [Internet] [cited 2016 Aug 31]. Available from: URL: http://www.searo.who.int/entity/vector_borne_tropical_diseases/data/data_factsheet/en/
7. Ho TS, Wang SM, Lin YS, et al. Clinical and laboratory predictive markers for acute dengue infection. J Biomed Sci 2013;20:75.
8. Liu JW, Lee IK, Wang L, et al. The usefulness of clinical practice based laboratory data in facilitating the diagnosis of dengue illness. Bio Med Res Int 2013;2013:198797.
9. Lai WP, Chien TW, Lin HJ, et al. A Screening tool for dengue fever in children. Pediatr Infect Dis J 2013;32(4):320-324.
10. Daumas RP, Passos SR, Oliveira RV, et al. Clinical and laboratory features that discriminate dengue from other febrile illnesses: a diagnostic accuracy study in Rio de Janeiro, Brazil. BMC Infect Dis 2013;13:77.
11. Cucunawangsih, Dewi BE, Sungono V, et al. Scoring Model to Predict Dengue Infection in the Early Phase of Illness in Primary Health Care Centre. [cited 2016 June 30]; Arch Clin Microb. 2015 6:2. Available from: URL: http://www.acmicrob.com.
12. Shih-Tien Pan, Po-AnSu, Kuo-TaiChena, et al. Comparison of the clinical manifestations exhibited by dengue and nondengue patients among children in a medical center in southern Taiwan. Acute Med 2014;4(2):53-6.
13. Watt G, Jongsakul K, Chouriyagune C, et al. Differentiating dengue virus infection from scrub typhus in Thai adults with fever. Am J Trop Med Hyg 2003;68(5):536-8.
14. Epelboin L, Boulle C, Ouar-Epelboin S, et al. Discriminating malaria from dengue fever in endemic areas: clinical and biological criteria, prognostic score and utility of the c-reactive protein: a retrospective matched-pair study in French Guiana. PLoS Negl Trop Dis 2013:7(9):e2420.

15. CDC DoV-BD. Dengue: Clinical Guidance. 2016 Jan 20. [cited 2017 Jan 22]. Available from: URL: https://www.cdc.gov/dengue/clinicalLab/laboratory.html
16. Kalayanarooj S, Nimmannitya S. A Study of erythrocyte sedimentation rate in dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health 1989;20(3):325-30.
17. Souza LJ, Reis AF, de Almeida FC, et al. Alteration in the erythrocyte sedimentation rate in dengue patients: analysis of 1,398 cases. Braz J Infect Dis 2008;12(6):472-5.
18. Halstead SB. Dengue. Lancet 2007;370:1644-52.
19. Samanta J, Sharma V. Dengue and its effects on liver. World J Clin Cases 2015;3(2):125-31.
20. Fernando S, Wijewickrama A, Gomes L, et al. Patterns and causes of liver involvement in acute dengue infection. BMC Infect Dis 2016;16:319.
21. Kuo HJ, Lee IK, Liu JW. Analyses of clinical and laboratory characteristics of dengue adults at their hospital presentations based on the World Health Organization clinical-phase framework: Emphasizing risk of severe dengue in the elderly. J Microbiol Immunol Infect 2017:S684-1182(17)30067-1.